REMARKS

This amendment is submitted in an earnest effort to bring this case to issue without delay.

Applicants have canceled claims 1 through 18 and are submitting new claims 19 through 52. Antecedent basis for the new claims may be found in the specification on pages 4 through 10. Thus claims 19 through 52 are now in the application and are presented for examination.

Applicants wish to reiterate their claim to the benefit of their Danish priority date of 28 May 1999 pursuant to the International Convention. Applicants have amended the CROSS REFERENCE TO RELATED APPLICATIONS to state that the present application is a continuation of copending application 09/980,029 filed 26 December 2001, now US Patent 6,682,742, which is the US National Phase of PCT/EP00/04786 filed 25 May 2000 and which claims the benefit of the priority of Danish Patent Application PA 19 99 00753 filed 28 May 1999. Applicants note that page 5 of the New Application Transmittal filed with the US Patent and Trademark Office on 23 September 2003 with the instant application stated that Applicants intended to rely on the benefit of both the International Filing Date of both EP00/04786 filed 25 May 2000 and the priority date of Danish Patent Application PA199900753 filed 28 May 1999. Furthermore in the filing receipts mailed 16 December 2003 and 11 August 2004 the US Patent and Trademark Office

recognized Applicants' claim to the priority of both EP00/04786 filed 25 May 2000 and the priority date of Danish Patent Application PA199900753 filed 28 May 1999. Now that Applicants have amended the cross reference to comply with the requirements of 37 CFR 1.78(a), it is believed that they have perfected their right to rely on the priority of the Danish Patent Application.

Applicants enclose a terminal disclaimer signed in their behalf by the undersigned attorney. It is believed that submission of the terminal disclaimer obviates the issue of potential double patenting of the obviousness type between the claims of the present invention and the claims in US Patent 6,682,742.

Now that Applicants have perfected their right to rely on the benefit of their Danish priority date of 28 May 1999 and their international filing date of 25 May 2000, no rejection of any claim now presented should be maintained under 35 USC 102(b) as anticipated by Applicants' own WO 00/73476, published 7 December 2000, which is itself the international application that corresponds to the instant US National Phase.

The Examiner has rejected claims 1 through 6 under 35 USC 102(b) as anticipated by ANTOINE et al (U). The Examiner argues that the reference discloses the entire genome of MVA and inherently there must be disclosure of DNA segments of at least 200 consecutive base pairs within Applicants' SEQ ID NO:1, and a number of restriction sites into which heterologous DNA could be inserted as well as a number of potential cloning sites within the ATI

region of the MVA genome for insertion of the heterologous DNA sequences.

Applicants have canceled claims 1 through 6 directed to DNA sequences and to vectors containing the DNA sequences and have replaced those claims with new claims 19 through 36. ANTOINE et al discloses the whole MVA genome with no indication or suggestion of isolating either SEQ ID NO:1, a fragment thereof containing at least 200 consecutive base pairs of SEQ ID NO:1 or a sequence that hybridizes under stringent conditions, as defined in the specification, to the nucleic acid of SEQ ID NO:1. Applicants are not claiming the whole MVA genome, but are claiming limited segments of DNA that are neither disclosed nor suggested in ANTOINE et al. It is especially important to note that there is no disclosure in ANTOINE et al of a nucleic acid segment taken from the ATI region of MVA that includes at least one restriction enzyme recognition site as an insertion site for a heterologous sequence and that hybridizes under stringent conditions to the nucleic acid sequence of SEQ ID NO:1 or its complementary strand, or of an isolated fragment of a nucleic acid sequence from the ATI region of modified vaccinia Ankara virus consisting essentially of at least 200 base pairs of the nucleic acid sequence that is SEQ ID NO:1, that is at least 70% homologous to SEQ ID NO:1 said nucleic acid sequence or isolated fragment capable of integration of the heterologous sequence through homologous recombination into the ATI region of an orthopoxvirus without interfering with its viral propagation or replication efficiency. Accordingly it is believed

that there is no basis to reject any claim now presented as anticipated under 35 USC 102 by ANTOINE et al. Furthermore since there is no suggestion in ANTOINE et al of the presently claimed invention, there is no basis to reject any claim now presented as obvious under 35 USC 103.

The ALTENBURGER patent discloses MVA as well as recombinant forms thereof. There is, however, no disclosure or suggestion of obtaining from the ATI region of MVA the nucleic acid sequence that is SEQ ID No:1 or a nucleic acid that hybridizes under stringent conditions to SEQ ID NO:1 or a fragment of at least 200 consecutive base pairs of SEQ ID NO:1 with its critical insertion site and using such a nucleic acid to integrate a heterologous sequence into the ATI region of an orthopoxvirus through homologous recombination to obtain an integrated recombinant orthopoxvirus without interfering with its viral propagation or replication efficiency. ALTENBURGER discloses insertion of foreign DNA into the thymidine kinase gene region, a region known to be non-essential to the vaccinia virus. There is not the slightest suggestion to exploit the ATI region of MVA. Accordingly ALTENBURGER is believed to provide no basis to reject any claim now presented as either anticipated under 35 USC 102 or as obvious under 35 USC 103.

Applicants believe that no claim now presented should be rejected as anticipated under 35 USC 102 or as obvious under 35 USC 103 in view of either SHIDA et al or the PAOLETTI et al references. Each of these references discloses the ATI regions from cowpox and

vaccinia and not from MVA. The ATI region of MVA differs extremely and substantially from the ATI region of all other poxviruses, especially vaccinia viruses. Each of these references does disclose insertion of foreign DNA into the non-essential ATI regions of cowpox and vaccinia viruses, but not into the ATI region of MVA. In all claims now presented, including the isolated nucleic acid sequences of claims 19 through 22 and the vectors comprising the isolated nucleic acid sequences of claims 23 through 36, it is specified that these sequences are isolated from the ATI region of modified vaccinia Ankara virus and that these sequences include at least one restriction enzyme recognition site as an insertion site for a heterologous sequence. The PAOLETTI et al references furthermore are directed to preparing attenuated vaccines or inactivated immunogens by inserting heterologous sequences into the ATI region of cowpox or vaccinia as opposed to preparing live recombinant orthopoxviruses without interfering with the viral propagation or replication efficiency of the orthopoxvirus as in the present invention. Thus no claim now presented should be regarded as anticipated by either SHIDA et al or the PAOLETTI et al references.

Applicants note that the Examiner has lined up a segment of SEQ ID NO: 1 against arbitrarily picked segments of DNA as shown in SHIDA and in PAOLETTI et al and has shown some homology in a given region between those segments and SEQ ID NO: 1. However, neither SHIDA et al nor PAOLETTI et al discloses an <u>isolated</u> fragment of a nucleic acid sequence from the <u>ATI region of modified</u>

vaccinia Ankara virus consisting essentially of at least 200 base pairs of the nucleic acid sequence that is SEQ ID NO:1, that is at least 70% homologous to SEQ ID NO:1 and that includes at least one restriction enzyme recognition site as an insertion site for a heterologous sequence, said isolated fragment of a nucleic acid sequence capable of integration of the heterologous sequence through homologous recombination into the ATI region of an orthopoxvirus without interfering with its viral propagation or replication efficiency. The DNA disclosed in each of SHIDA et al and PAOLETTI et al contains many more base pairs than the entire sequence that is SEQ ID NO:1 and it is not seen that there is at least 70% homology between the entire length of any of these large sequences disclosed in the references and SEQ ID NO: 1 or any fragment thereof comprising at least 200 base pairs. Nor has the Examiner pointed to any specific restriction enzyme recognition site as an insertion site for a heterologous sequence in either the SHIDA et al sequence or the PAOLETTI et al sequence.

The ATI region of MVA differs from the ATI region of all other vaccinia viruses in that thee wild type poxvirus itself deleted parts of the non-essential ATI gene and, thus, parts of a superfluous region within its genome which was obviously not necessary for replication and generation of new viruses. Foreign genes are of course also superfluous for the virus and in no way essential for the viral life cycle. Since the ATI region of MVA has proven to be unstable even for viral genes, one skilled in the art would have expected that when inserting foreign genes into that

region, these genes would of course also be deleted, during further replication cycles. See page 386, right-hand column or ANTOINE et al showing the instability in the right terminal region of the MVA ATI. Further MEYER et al, Journal of General Virology, 72, pp 1031-1038 (1991) on page 1036, right-hand column, lines 2 through 4 indicates regarding MVA: "Additionally both terminal regions can readily undergo complex sequence rearrangements or transpositions during continuous propagation in cell cultures." A copy of MEYER et al is enclosed. Note that this reference was cited during the prosecution of the parent application and in the examination of the corresponding International Application. Thus one skilled in the art would not have expected that a genomic region newly created by natural deletions would be suitable for stable integration of foreign genes. However, Surprisingly, Applicants have found that the foreign (heterologous) genes may be stably integrated into the ATI regions of a number of orthopoxviruses, including MVA, by employing the vectors claimed according to the present invention that include the presently claimed sequences isolated from the ATI region of modified vaccinia Ankara virus and which include at least one restriction enzyme recognition site as an insertion site for a heterologous sequence (foreign gene).

Nor does any combination of ANTOINE et al, ALTENBURGER, SHIDA et al and the PAOLETTI et al references suggest any of the claims as now presented in view of the disclosure in ANTOINE et al and MEYER et al of the known instability in the ATI region of MVA. Applicants do not agree that it would be obvious to use a sequence

taken from the ATI region of MVA as a vector for integration of a heterologous sequence into the ATI region of MVA or any other orthopoxvirus. Page 388 of ANTOINE et al does not suggest that the ATI region of MVA is very similar to that of conventional vaccinia viruses or NYVAC. ANTOINE et al discloses only that MVA and NYVAC share ATI remnant ORF A26L. ANTOINE et al additionally confirms on page 388, right-hand column, first paragraph, last sentence, that despite similarities between MVA and NYVAC, the two viruses have a clearly different genetic background. There is no disclosure or suggestion in ANTOINE of insertion of heterologous sequences into the unstable ATI region of MVA and its subsequent integration into the ATI region of an orthopoxvirus by homologous recombination. Furthermore the wild-type NYVAC used in PAOLETTI et al still contains a stable integrated ATI gene; the ATI remnant was not created by the virus itself by natural deletion, but was engineered, that is artificially deleted for insertion of foreign genes into this region. Accordingly, in NYVAC this region is stable and thus, suitable for insertion of foreign genes and is in no way comparable to the unstable ATI region of MVA.

As explained above both ANTOINE et al and MEYER et al disclose that the ATI region of MVA is unstable and so one "skilled in the art" would not be motivated to attempt to insert heterologous sequences into this ATI region to create a vector suitable for integrating the heterologous sequence into the ATI region of an orthopoxvirus by homologous recombination. In spite of the prior art teaching of the instability of this MVA ATI region

Applicants have been able to use the presently claimed vectors derived from this ATI region to integrate heterologous sequences into the ATI region of orthopoxviruses by homologous recombination to produce integrated recombinant orthopoxviruses. Such would not have been expected by those skilled in the art and is a basis for patentable invention.

Im view of the above, it is believed that claims 19 through 22 directed to particular nucleic acids obtained from the ATI region of MVA and containing at least one restriction site suitable as an insertion site for heterologous sequences are patentable over the cited prior as well as the vectors of claims 23 through 36 which contain these nucleic acids. In addition the claims to integrated recombinant orthopoxviruses and to integrated recombinant orthopoxviruses that are prepared using the vectors of claims 23 to 36 to integrate the heterologous sequences into the orthopoxviruses through homologous recombination and a process to prepare the integrated recombinant orthopoxviruses through homologous recombination using these vectors should be patentable as well. Furthermore the pharmaceutical compositions containing the recombinant orthopoxviruses as pharmaceutically active ingredients and method of use claims employing these recombinant orthopoxviruses to effect an immune response should also be patentable as none of these claims is directed to subject matter that is anticipated or obvious in view of the cited prior art.

Favorable action in this case is earnestly solicited. Applicants enclose Forms PTO 2038 to pay for the filing of the terminal disclaimer, to pay for the new claims in excess of three independent claims and twenty total claims, and to pay for the petition to obtain a one month extension of the term for response.

Respectfully submitted,
The Firm of Karl F. Ross P.C.

By: Jonathan Myers, 26,963
Attorney for Applicant

Enc: Terminal Disclaimer
PTO 2038 (Terminal Disclaimer)
PTO Form 1449 and Reference
Petition for Extension
PTO 2038 (Petition for Extension)
PTO 2038 (Additional Claims)

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5676 Riverdale Avenue Box 900
Bronx, NY 10471-0900
Cust. No.: 535
Tel: (718) 884-6600
Fax: (718) 601-1099

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